Seizure 18 (2009) 630–633

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Analysis of factors influencing admission to intensive care following convulsive status epilepticus in children

Sandya Tirupathi [a,b], Joseph B. McMenamin [a,b], David W. Webb [a,*]

[a] Department of Neurosciences, Our Lady's Hospital for Children, Crumlin, Dublin 12, Ireland
[b] Department of Paediatrics, Royal College of Surgeons in Ireland Medical School, St Stephen's Green, Dublin 1, Ireland

ARTICLE INFO

Article history:
Received 17 March 2009
Received in revised form 8 June 2009
Accepted 16 July 2009

Keywords:
Febrile seizures
Respiratory insufficiency
Protocol
Guidelines
Pre-hospital treatment

ABSTRACT

Objectives: To identify clinical features and therapeutic decisions that influence admission to the Intensive Care unit (ICU) in children presenting with convulsive status epilepticus (CSE).
Methods: We evaluated 47 admissions with status epilepticus to a tertiary paediatric hospital A&E over a three year period (2003–2006). Following initial management 23 episodes required admission to ICU and 24 were managed on a paediatric ward. We compared clinical, demographic data and compliance with our CSE protocol between the ICU and ward groups.
Results: Median age at presentation in the ICU group was 17 months (range 3 months–11 years) compared to 46 months in the ward group (range 3 months–10 years). Fifty per cent of patients in both groups had a previous history of seizures. Median duration of pre-hospital seizure activity was 30 min in both groups. More than two doses of benzodiazepines were given as first line medication in 62% of the ICU group and 33% of the ward group. Among children admitted to ICU with CSE, 26% had been managed according to the CSE protocol, compared to 66% of children who were admitted to a hospital ward. Febrile seizures were the most common aetiology in both groups.
Conclusion: Younger age at presentation, administration of more than two doses of benzodiazepines and deviation from the CSE protocol appear to be factors which influence admission of children to ICU. Recognition of pre-hospital administration of benzodiazepines and adherence to therapeutic guidelines may reduce the need for ventilatory support in this group.

1. Introduction

Convulsive status epilepticus (CSE) is a series of generalised tonic-clonic seizures without intervening recovery or a continuous seizure over a period of 30 min. The duration of what defines a status epilepticus, in adults and children aged more than 5 years, has been progressively being reduced from 30 min to an operational definition of 5 min.[1] The concept is the same in both children and adults. Most seizures stop spontaneously within five minutes.[2] Seizures persisting beyond five minutes have the potential to evolve into CSE[3] and delays in initiating treatment are associated with a mortality of 14% for young adults (16–59 years) and 38% for elderly (60 years and above).[4] CSE in children has a mortality of 4%[5] with higher morbidity and mortality when there is a delay in treatment.[6–9] Early treatment is therefore a priority.

The causes of CSE in adults[4] are different from childhood CSE. The main causes in adults are low blood concentrations of antiepileptic drugs (AEDs) in patients with chronic epilepsy (34%), remote symptomatic causes (24%), and remaining being acute symptomatic causes (52%) which include cardiovascular accidents (22%), anoxia or hypoxia (10%), metabolic causes (10%) and alcohol withdrawal (10%). In children the single main cause of CSE is febrile convulsion. Many treatment protocols exist due to very few controlled double-blind clinical studies. In adults and children the principle is the same with early use of benzodiazepines followed by a long acting anticonvulsant if convulsive activity continues. EFNS guidelines[10] for adult status epilepticus outlined the preferred treatment pathway for generalised convulsive status epilepticus (GCSE) as intravenous (i.v.) administration of 4 mg of lorazepam or 10 mg of diazepam directly followed by 15–18 mg/kg of phenytoin or equivalent fosphenytoin. If seizures continue for more than 10 min after first injection another 4 mg of lorazepam or 10 mg of diazepam is recommended. Refractory GCSE is treated by anaesthetic doses of midazolam, propofol or barbiturates; the anaesthetics are titrated against an electroencephalogram burst suppression pattern for at least 24 h. In adults thiamine 100 mg IV and glucose infusions for hypoglycaemia are considered prior to AED therapy. The main differences in the existing protocols in adult and paediatric patients are in the sequence of AED therapy and in the choice of the second line agent. Current Advanced

* Corresponding author. Tel.: +00 353 14096413; fax: +00 353 14096887.
E-mail address: david.webb@olchc.ie (D.W. Webb).

1059-1311/$ – see front matter © 2009 Published by Elsevier Ltd on behalf of British Epilepsy Association.
doi:10.1016/j.seizure.2009.07.006

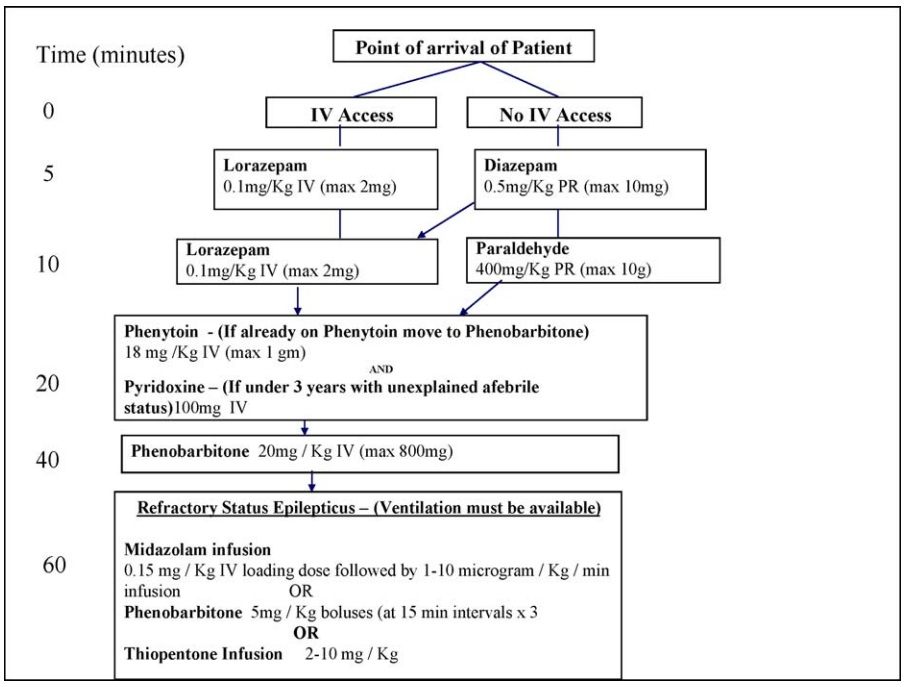

Fig. 1. CSE Protocol in our hospital.

Paediatric Life Support (APLS) guidelines recommend per rectal paraldehyde therapy as a second line agent after benzodiazepines and before phenytoin.

Our protocol for CSE management in children has been in place since 1998[11] (Fig. 1). It is similar in principle to the UK Status Epilepticus Working Party proposed protocol[3] and differs from the APLS guidelines in the use of paraldehyde only. Previous reports suggest that admission to ICU of children with CSE may be related to inappropriate management[8,12,13] and specifically to the excessive use of benzodiazepines.[8,13–15] We sought to assess the factors that influenced admission to ICU in our cohort.

Our objectives were:

(1) To compare the clinical details, pre-hospital and emergency hospital management of children with CSE admitted to ICU (ICU group) with those admitted to the hospital ward (ward group).
(2) To evaluate the compliance with the hospital CSE protocol in these two groups and in particular to assess the use of benzodiazepines and second line AEDs.
(3) To identify factors that may have led to admission to ICU and suggest strategies to reduce this need.

1.1. Methods

Children presenting between 2003 and 2006 with seizures to A&E and requiring admission to ICU were identified through the hospital ICU database. Only those with confirmed CSE who had presented to our A&E department were included for analysis.

Twenty-three admissions identified among 19 children represented the ICU group. A random selection of children presenting with CSE presenting to the A&E department, who did not require admission to ICU, was made from a child neurology database for the same time period. Twenty-four admissions among 22 children represented the ward group.

CSE was defined as a generalised tonic-clonic seizure or multiple seizures without intervening consciousness, lasting 30 min or longer. Patient records were reviewed for clinical and demographic data including—date of birth, sex, age at presentation with CSE, background history, seizure history, medication history, febrile seizure history, associated co-morbidities, mode of transport to hospital, pre-hospital seizure duration, pre-hospital rescue AEDs, in-hospital AEDs, number of doses of benzodiazepines, choice and timing of second line agents (phenytoin, or paraldehyde as in protocol and other e.g. phenobarbitone or midazolam infusion), ventilation requirement and indication for ICU admission. Management of the patients was compared to the hospital protocol (Fig. 1). Admissions that received no more than 2 doses of benzodiazepines and were administered second line agent if required within 30 min of arrival were deemed to have been managed as per protocol. CSE aetiology was classified as acute symptomatic, febrile status, remote symptomatic and idiopathic epilepsy related CSE[16] by consensus between the authors.

2. Results

The clinical, demographic and management details are outlined in Table 1.

Table 1
Comparative data between the ICU and Ward groups.

	ICU($n=23$)	WARD ($n=24$)	p value
Median age	17months*	46 months*	
Male to female ratio	9:10 (1:1.1)	10:12 (1:1.2)	$p>0.05$
Previous FS history	5/23	4/24	$p>0.05$
Known epilepsy	8/23	8/24	$p>0.05$
Seizure duration (pre-hosp)	30 min	30 min	
Pre-hospital rescue AED	9/23 (39%)	7/24 (29%)	$p>0.05$
Dose pre-hospital (mean)	8.8 mg	6.4 mg	
Ambulance transport	13/23	11/24	$p>0.05$
Rescue in ambulance	0	0	
>2 doses of BZD	15/23 (65%)	8/24 (33%)	$p<0.05$ (0.028)
Early second line AED	12/22 (54%)	9/14 (64%)	$p=0.31$
Compliance with protocol	6/23 (26%)	16/24 (66%)	$p<0.05$ (0.005)

FS: febrile seizure, and BZD: benzodiazepine.
* 3 months–11 years.

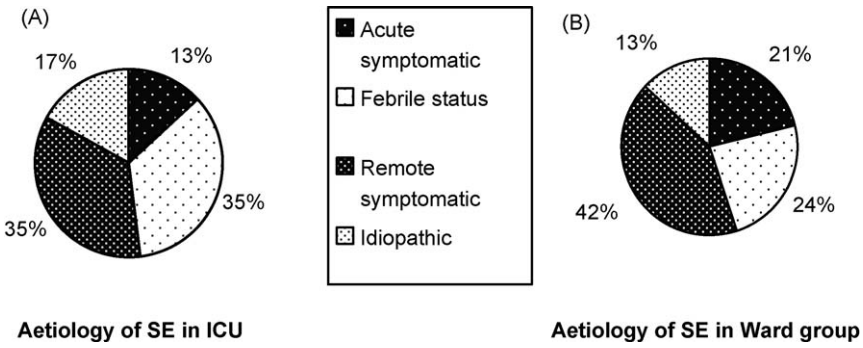

Fig. 2. Comparison of aetiology in two groups.

2.1. Clinical details

Median age at presentation in the ICU group was 17 months (range 3 months–11 years) with 70% under three years of age and 46 months (range 3 months–10 years) in the ward group. The gender ratio was equal. One girl with epilepsy aged two years had four admissions and another girl had two admissions to ICU.

A previous history of seizures was present in 56% (13/23) of the ICU group and 50% (12/24) of ward admissions. It was the first seizure in 43% (10/23) in ICU group and 50% (12/24) in ward group. Median duration of seizures pre-hospital was 30 min in both groups (range 5 min–2 h). Ambulance transport was used in 56% (13/23) of the ICU group and 45% (11/24) of the ward group. The causes of CSE are outlined in Fig. 2.

2.2. Pre-hospital management

Pre-hospital rescue medication was given in 39% (9/23) of the ICU group and 29% (7/24) of the ward group, all of whom had a previous seizure history. Four of the ICU and five of the Ward group with a prior history of seizures did not receive pre-hospital rescue therapy. Seven of these had a history of febrile seizures. Seven children who had received the rescue medications did so at home prior to transfer. No child received rescue medication during ambulance transfer.

In the ICU group, the dose of pre-hospital rescue therapy ranged from 5 mg to 15 mg of Diazepam, buccal Midazolam or both (mean 8.8 mg). In the ward group the dose of rescue therapy ranged from 5 mg to 10 mg of Diazepam, buccal Midazolam or both (mean 6.4 mg).

2.3. In-hospital management

The AED usage and seizure termination are outlined in Tables 2 and 3. Indications for ICU admission and timing of ventilation are outlined in Table 4.

Three or more doses of benzodiazepines were administered in 65% (15/23) of the ICU group and 33% (8/24) of the ward group. This included pre-hospital benzodiazepine administration. All those who received pre-hospital rescue medication went on to receive more than two doses of benzodiazepines. Administration of a third dose of benzodiazepine resulted in seizure termination in only 3 of the 23 (13%).

The timing of second choice drug usage was not significantly different between the ICU and Ward groups (54% vs 64%). However the preferred second choice AED was phenytoin in 63% of the ICU group and 85% of the ward group. Compliance with the protocol was 26% (6/23) in the ICU group and 66% (16/24) in the ward group ($p = <0.005$). Repeated administration of benzodiazepines appeared to be the predominant factor in non-adherence to the protocol in both groups.

Table 2
Comparison of AED use in ICU and ward groups.

First line AED was benzodiazepines in all admissions	ICU (23)	Ward (24)
Two or less doses of BZD	8	16
More than 2 doses of BZD	15	8
Second line AED in	ICU (22)	Ward (14)
PHT	14	12
Paraldehyde	4	2
PHB	2	0
Midazolam infusion	2	0
Third line AED	ICU (16)	Ward (5)
BZD loraz/midazolam infusion	7	0
PHB	5	4
PHT	3	1
Paraldehyde	1	0

Table 3
Seizure termination in ward group ($n = 24$).

Sz terminated with first line:	
• With 2 or less doses of BZD	7
• With addition of 3rd dose	3
Sz terminated with addition of second line	
• With addition of PHT	8
• With addition of paraldehyde	1
Sz terminated with addition of 3rd line	
• With addition of PHB to PHT	4
• With addition of PHT to paraldehyde	1

56% (13/23) of patients were admitted to ICU because of respiratory compromise. 76% (10/13) of these had received >2 doses of benzodiazepines of whom 30% (4/13) had received pre-hospital benzodiazepines. The remainder were admitted because of refractory status or for observation.

Table 4
IPPV use and indication for ICU.

Timing of IPPV in ICU patients	$n = 23$	Indication for ICU admission
Before 2nd line AED	6*	Respiratory compromise
After the 2nd line AED	7*	Respiratory compromise
After 3rd line	7	Refractory status
None	3	Admitted for observation
Sz termination in ICU group	**$n = 23$**	
Apparent Sz termination with 1st line		1 (ventilated but no other AED)
Apparent Sz termination with 2nd line:		6 (did not receive 3rd line AED)
Definite sz termination with 3rd line		3 (observed with no ventilation)
Timing unclear		13 (none had EEG confirmation)

* Of the 13 admitted with respiratory compromise 10 had >2 doses of benzodiazepines.

3. Discussion

We set out to identify the clinical features and therapeutic decisions that might influence admission to ICU in children presenting with CSE. In this retrospective study all the children were admitted through the same accident and emergency department with an established CSE protocol. We have compared those children with CSE admitted to ICU with those admitted to the ward and found no differences in gender, medical or seizure history, pre-hospital management or seizure duration. The profile of aetiological factors was comparable to other studies of childhood CSE.[12,17,18]

None of our admissions had received medical treatment of their CSE during ambulance transfer. This included nine admissions of children with a prior history of seizures including one with a previous history of CSE. Given that the median pre-hospital duration was 30 min this represents an important missed therapeutic opportunity. We believe there is a role for education of all ambulance crew in the administration of rescue therapy for children with CSE particularly as the use of buccal midazolam is now easier, more effective and socially more acceptable than rectal diazepam.[19,20]

Pre-hospital rescue therapy for CSE is of proven benefit.[21] However most existing guidelines including the APLS and status epilepticus working party protocol for management of CSE do not include or consider *pre-hospital* treatment or seizure duration. In our study all those who were treated with pre-hospital benzodiazepine received at least 3 doses. Only 13% of this group achieved seizure control confirming previous observations that multiple doses of benzodiazepines are of limited value in CSE.[9,22] Future guidelines should include *pre-hospital* treatment to avoid excessive use of benzodiazepines and its consequences and limit the use of benzodiazepines to two doses.

The commonest reason for admission to ICU following CSE in this study was respiratory compromise and this has been observed in other similar studies.[8,14,15] Children admitted to ICU were more likely to have received more than two doses of a benzodiazepine and 70% of children admitted to ICU in our study were less than three years of age. Our data suggests that children under three years appear to be at more risk of respiratory compromise from benzodiazepine overuse.

Current guidelines with two arms contribute to the excessive use of benzodiazepines and should perhaps be confined to a single pathway. Furthermore the guidelines fail to take into account the pre-hospital seizure duration.

The current trend to shorten the definition of CSE would suggest that we should be considering second line agents earlier. In our opinion intravenous phenytoin should be given without delay to any child who has been convulsing for 20 min even if this has been in the pre-hospital setting.

4. Conclusions

Consideration should be given to education of ambulance crews in the use of rescue therapy for CSE. Young children in particular with CSE who receive more than two doses of benzodiazepines are at high risk of requiring assisted ventilation and intensive care. In-hospital guidelines for management of CSE should take into consideration pre-hospital administration of benzodiazepines and seizure duration. We believe intravenous phenytoin should be given to all children when seizure activity lasts 20 min or more irrespective of what prior treatment has been administered.

Acknowledgements

None.
Funding: None.

Conflict of interest

None.

References

1. Meldrum BS. The revised operational definition of generalised tonic-clonic status epilepticus in adults. *Epilepsia* 1999;**40**:120–2.
2. Smith RA, Martland T, Lowry MF. Children with seizures presenting to accident and emergency. *J Accid Emerg Med* 1996;**13**:54–8.
3. The Status Epilepticus working Party. The treatment of convulsive status epilepticus in children. *Arch Dis Child* 2000;**83**:415–9.
4. Delorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective population based epidemiological study of status epilepticus in Richmond. *Neurology* 1996;**46**:1029–35.
5. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics* 1989;**83**:323–31.
6. Shorvon SD. Tonic–clonic status epilepticus. *J Neurol Neurosurg Psychiatry* 1993;**56**:125–34.
7. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalised convulsive status epilepticus. *New Engl J Med* 1998;**339**:792–8.
8. Chin RFM, Neville BGR, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *Lancet Neurol* 2008;**7**:696–703.
9. Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. *Brain Res* 1998;**814**:179–85.
10. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. *Eur J Neurol* 2006;**13**:445–50.
11. Najam Y, McDonald DG, Keegan M, Webb DW, McMenamin JB. *Ir Med J* 2004;**97**:246–8.
12. Chin RFM, Verhulst L, Neville BGR, Peters MJ, Scott RC. Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J Neurol Neurosurg Psychiatry* 2004;**75**:1584–8.
13. Tobias JD, Berkenbosch JW. Management of status epilepticus in infants and children prior to paediatric ICU admission: deviations from the current guidelines. *S Med J* 2008;**101**:268–72.
14. Stewart WA, Harrison R, Dooley JM. Respiratory depression in the acute management of seizures. *Arch Dis Child* 2002;**87**:225–6.
15. Norris E, Marzouk O, Nunn A, McIntyre J, Choonara I. Respiratory depression in children receiving diazepam for acute seizures: a prospective study. *Dev Med Child Neurol* 1999;**41**:340–3.
16. Commission on epidemiology and prognosis, ILAE. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;**34**(4):592–596.
17. Neville BGR, Chin RFM, Scott RC. Childhood convulsive status epilepticus: epidemiology, management and outcome. *Acta Neurol Scand* 2007;**115**:21–4.
18. Hussain N, Appleton R, Thorburn K, Aetiology. course and outcome of children admitted to paediatric intensive care with convulsive status epilepticus: a retrospective 5-year review. *Seizure* 2007;**16**:305–12.
19. Wilson MT, Macleod S, O' Regan ME. Nasal/buccal midazolam use in the community. *Arch Dis Child* 2004;**89**:50–1.
20. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment in children: a randomized controlled trial. *Lancet* 2005;**366**:205–10.
21. O'Dell C, Shinnar S, Ballaban-Gil KR, Hornick M, Sigalova M, Kang H, et al. Rectal diazepam gel in the home management of seizures in children. *Pediatr Neurol* 2005;**3**:166–72.
22. Chen JWY, Naylor DE, Wasterlain CG. Advances in the pathophysiology of status epilepticus. *Acta Neurol Scand* 2007;**115**:7–15.